Lupus Nephritis Management

Where are we Now and where are we going?

Alaa Sabry., MD, FACP.

Assistant Professor of Nephrology

Urology and Nephrology Center

Mansoura University

The Road Map

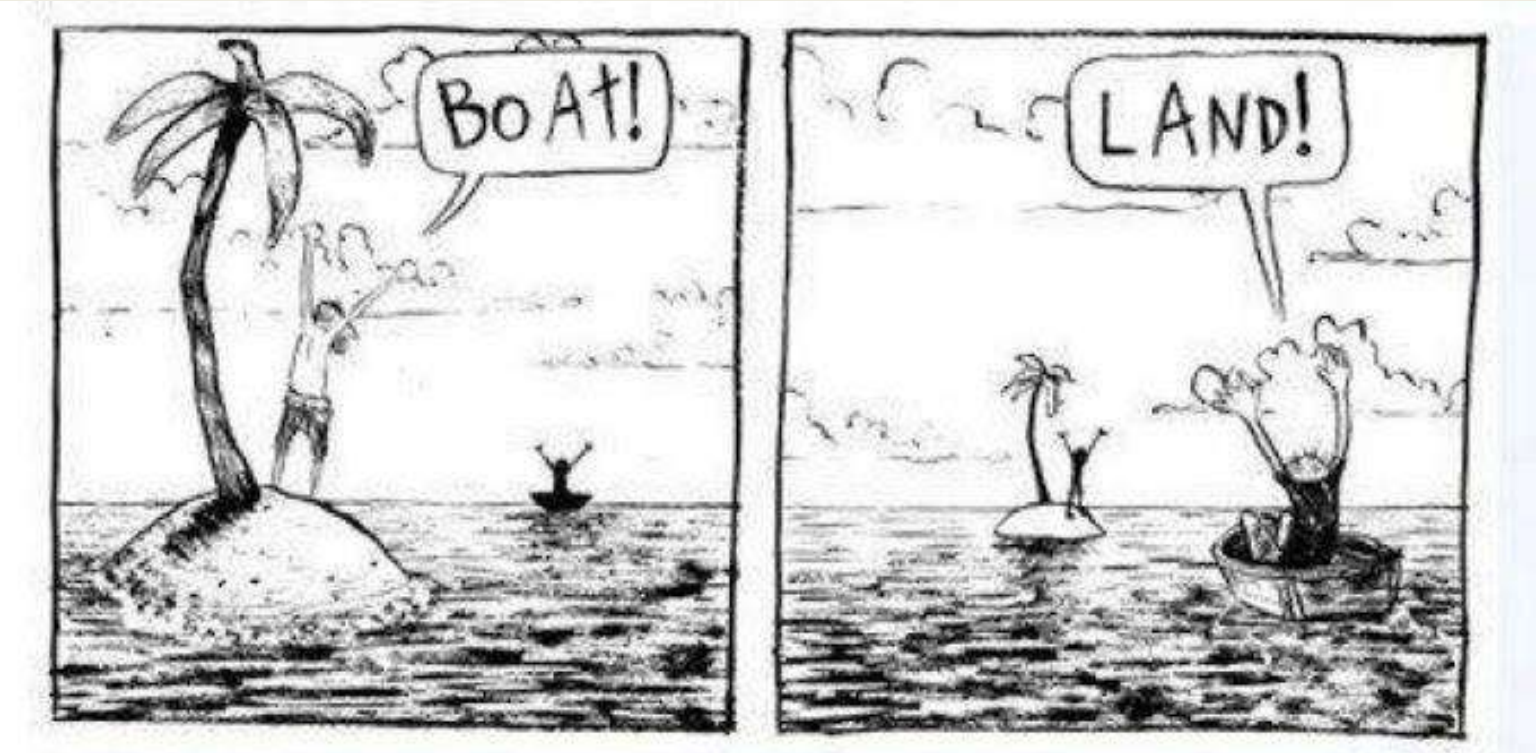
Histopathology of Lupus Nephritis

Conventional Therapies

Future Therapy

Conclusion

Evidence vs Logic



Logically both of us may be right,

BUT

What is the **EVIDENCE** for what will be better for us?

The Road Map

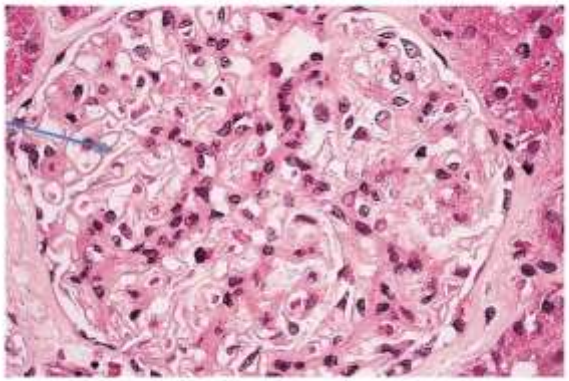
Histopathology of Lupus Nephritis

Lupus Nephritis ISN/RPS Classification

Class I	**Minimal mesangial lupus nephritis**
	Normal glomeruli by light microscopy, but mesangial immune deposits by immunofluorescence
Class II	**Mesangial proliferative lupus nephritis**
	Purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microsocpy, with mesangial immune deposits
	A few isolated subepithelial or subendothelial deposits may be visible by immunofluorescence or electron microscopy, but not by light microscopy
Class III	**Focal lupus nephritis[b]**
	Active or inactive focal, segmental or global endo- or extracapillary glomerulonephritis involving <50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations
Class III (A)	Active lesions: focal proliferative lupus nephritis
Class III (A/C)	Active and chronic lesions: focal proliferative and sclerosing lupus nephritis
Class III (C)	Chronic inactive lesions with glomerular scars: focal sclerosing lupus nephritis
Class IV	**Diffuse lupus nephritis[b]**
	Active or inactive diffuse, segmental or global endo- or extracapillary glomerulonephritis involving ≥50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class is divided into diffuse segmental (IV-S) lupus nephritis when ≥50% of the involved glomeruli have segmental lesions, and diffuse global (IV-G) lupus nephritis when ≥50% of the involved glomeruli have global lesions. Segmental is defined as a glomerular lesion that involves less than half of the glomerular tuft. This class includes cases with diffuse wire loop deposits but with little or no glomerular proliferation.
Class IV-S (A)	Active lesions: diffuse segmental proliferative lupus nephritis
Class IV-G (A)	Active lesions: diffuse global proliferative lupus nephritis
Class IV-S (A/C)	Active and chronic lesions: diffuse segmental proliferative and sclerosing lupus nephritis
Class IV-G (A/C)	Active and chronic lesions: diffuse global proliferative and sclerosing lupus nephritis
Class IV-S (C)	Chronic inactive lesions with scars: diffuse segmental sclerosing lupus nephritis
Class IV-G (C)	Chronic inactive lesions with scars: diffuse global sclerosing lupus nephritis
Class V	**Membranous lupus nephritis**
	Global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations
	Class V lupus nephritis may occur in combination with class III or IV in which case both will be diagnosed
	Class V lupus nephritis may show advanced sclerosis
Class VI	**Advanced sclerotic lupus nephritis**
	≥90% of glomeruli globally sclerosed without residual activity

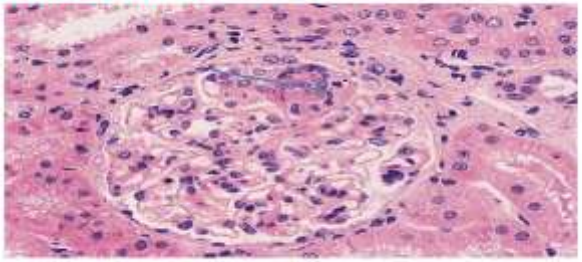
Indicate and grade (mild, moderate, severe) tubular atrophy, interstitial inflammation and fibrosis, severity of arteriosclerosis or other vascular lesions.
[a] Indicate the proportion of glomeruli with active and with sclerotic lesions.
[b] Indicate the proportion of glomeruli with fibrinoid necrosis and/or cellular crescents.

LUPUS NEPHRITIS CLASS II



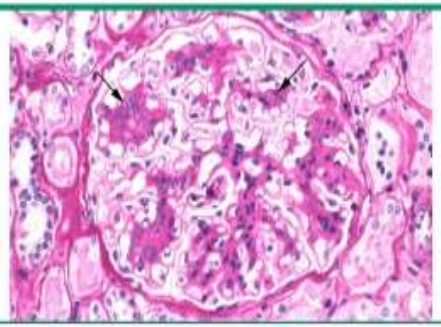
Mild global mesangial hypercellularity within capillary loops

LUPUS NEPHRITIS III



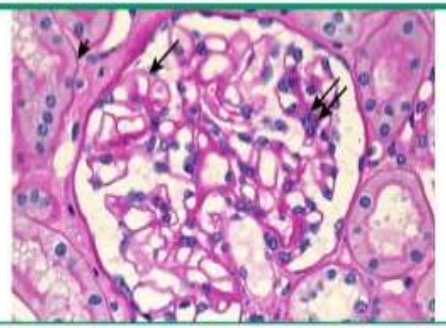
Focal endocapillary proliferative lesions on a background of focal

Light micrograph showing mesangial proliferative glomerulonephritis



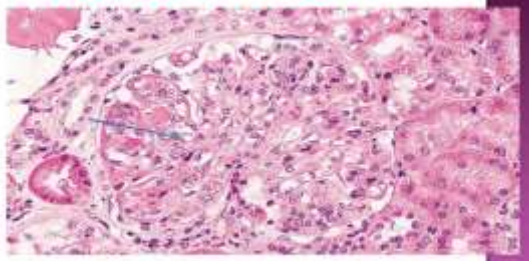
Light micrograph of a mesangial glomerulonephritis showing segmental areas of increased mesangial matrix and cellularity (arrows). This finding alone can be seen in many diseases, including lupus nephritis and IgA nephropathy.
Courtesy of Helmut Rennke, MD.

Normal glomerulus



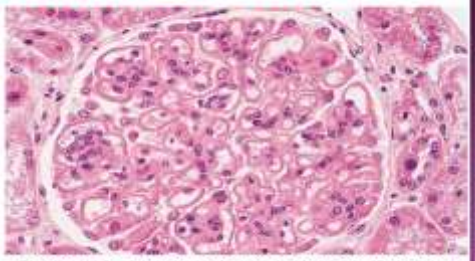
Light micrograph of a normal glomerulus. There are only 1 or 2 cells per capillary tuft, the capillary lumens are open, the thickness of the glomerular capillary wall (long arrow) is similar to that of the tubular basement membranes (short arrow), and the mesangial cells and mesangial matrix are located in the central or stalk regions of the tuft (arrows).
Courtesy of Helmut G Rennke.

LUPUS NEPHRITIS CLASS IV



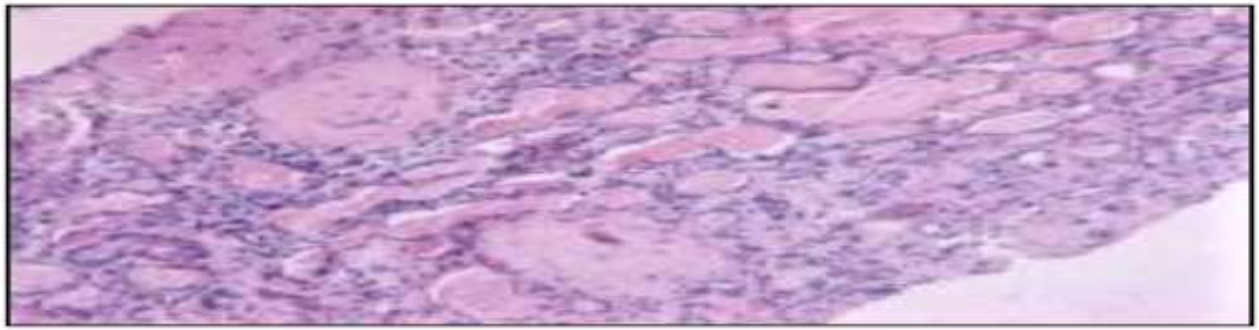
Glomerular capillary walls are segmentally thickened by wire-loop deposits. An intraluminal deposit forms a hyaline thrombus in one)capillary, and there is global endocapillary proliferation (arrow

LUPUS NEPHRITIS CLASS V



There is regular thickening and rigidity of the glomerular capillary walls accompanied by global mesangial hypercellularity

ADVANCED SCLEROSIS LUPUS NEPHRITIS CLASS VI



The Road Map

Histopathology of Lupus Nephritis

Conventional Therapies

Class III & IV Management

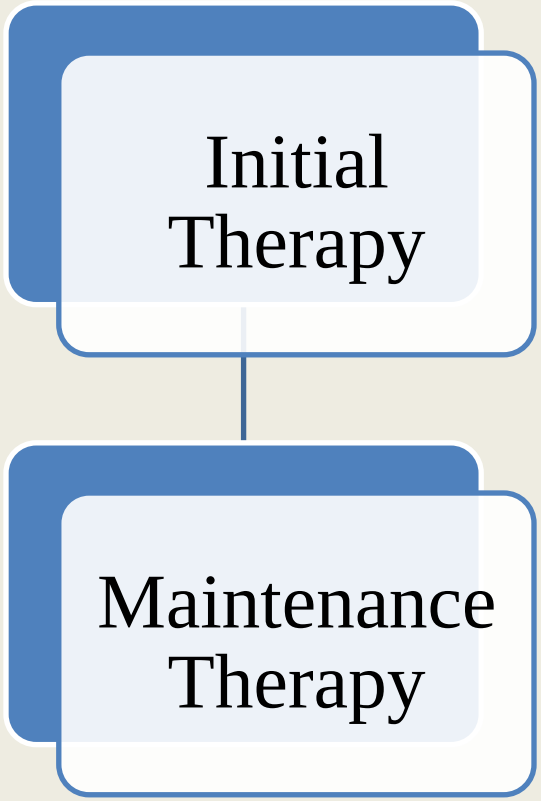
Overview

The evolution of initial therapy in proliferative LN has been to reduce toxicity while maintaining efficacy.

The objective is to rapidly decrease kidney inflammation by initial intensive treatment,

and then

consolidate treatment over a longer time.



Class I and Class II Lupus Nephritis management

Class I LN is not associated with long-term impairment of kidney function.

There are no evidence-based data on the treatment of class II LN.

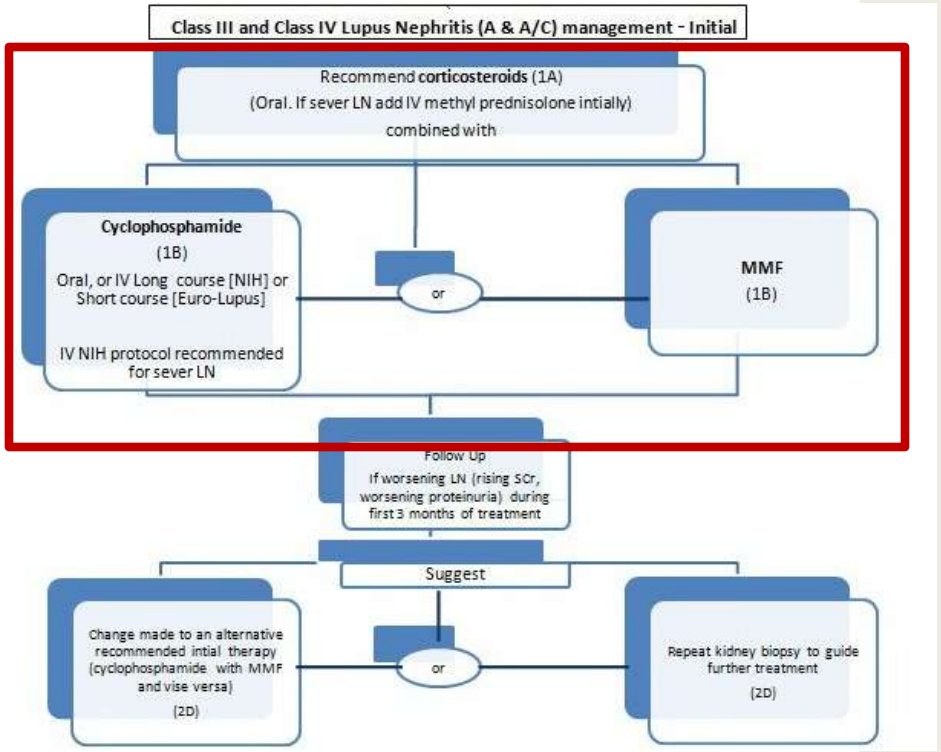
At present, there are no data to suggest that every patient with lupus requires a kidney biopsy, or that treatment of class I LN is clinically necessary.

While there have been no prospective studies of the treatment of nephrotic-range proteinuria in class II LN, it is reasonable to treat such patients as for MCD/FSGS in case of nephrotic syndrome, or if proteinuria cannot be controlled using RAS blockade.

Treatment Regimens

Initial Therapy - Class III & IV

Widely used regimens	Other regimens



All the above regimens are in addition of Corticosteroids.

Widely used regimens
Initial Therapy - Class III & IV

Table 28 | Regimens for initial therapy in class III/class IV LN

Regimen	A. NIH	B. Euro-Lupus
Cyclophosphamide	i.v. cyclophosphamide 0.5–1 g/m^2; monthly for 6 months	i.v. cyclophosphamide 500 mg; every 2 weeks for 3 months
MMF	—	—
Benefit shown by RCT in proliferative LN	Yes	Yes
Benefit shown by RCT in severe proliferative LN	Yes	Untested
Comments	Effective in whites, blacks, Hispanics, Chinese	Effective in whites. Untest in blacks, Hispanics, Chine

LN, lupus nephritis; MMF, mycophenolate mofetil; RCT, randomized controlled trial.
All regimens include corticosteroids:

- Oral prednisone, initial dose up to 0.5–1 mg/kg/d, tapering over 6–12 months according to cl
- i.v. methylprednisolone is sometimes added initially for severe disease.

The dosing and duration of corticosteroids has never been subject to evaluation by RCTs.

(A) NIH Regimen

The NEW ENGLAND JOURNAL of MEDICINE

Therapy of Lupus Nephritis

Howard A. Austin, III, M.D., John H. Klippel, M.D., James E. Balow, M.D., Nicole G.H. Le Riche, M.D., Alfred D. Steinberg, M.D., Paul H. Plotz, M.D., and John L. Decker, M.D.

N Engl J Med 1986; 314:614-619 | March 6, 1986 | DOI: 10.1056/NEJM198603063141004

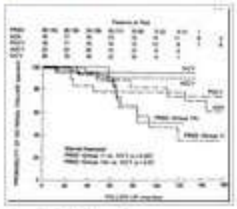
Share:

Abstract

We evaluated renal function in 107 patients with active lupus nephritis who participated in long-term randomized therapeutic trials (median follow-up, seven years). For patients taking oral prednisone alone, the probability of renal failure began to increase substantially after five years of observation. Renal function was better preserved in patients who received various cytotoxic-drug therapies, but the difference was statistically significant only for intravenous cyclophosphamide plus low-dose prednisone as compared with high-dose prednisone alone ($P = 0.027$). The advantage of treatment with intravenous cyclophosphamide over oral prednisone alone was particularly apparent in the high-risk subgroup of patients who had chronic histologic changes on renal biopsy at study entry. Patients treated with intravenous cyclophosphamide have not experienced hemorrhagic cystitis, cancer, or a disproportionate number of major infections. We conclude that, as compared with high-dose oral prednisone alone, treatment of lupus glomerulonephritis with intravenous cyclophosphamide reduces the risk of end-stage renal failure with few serious complications. (N Engl J Med 1986;314:614–9.)

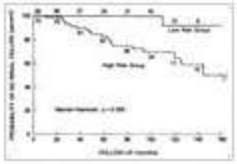
MEDIA IN THIS ARTICLE

FIGURE 1



Probability of Maintaining Life-Supporting Renal Function in 107 Patients with Active Lupus Nephritis, According to Treatment Group.

FIGURE 2



Probability of Maintaining Life-

Austin III HA et al. N Engl J Med 1986; 314: 614–619.

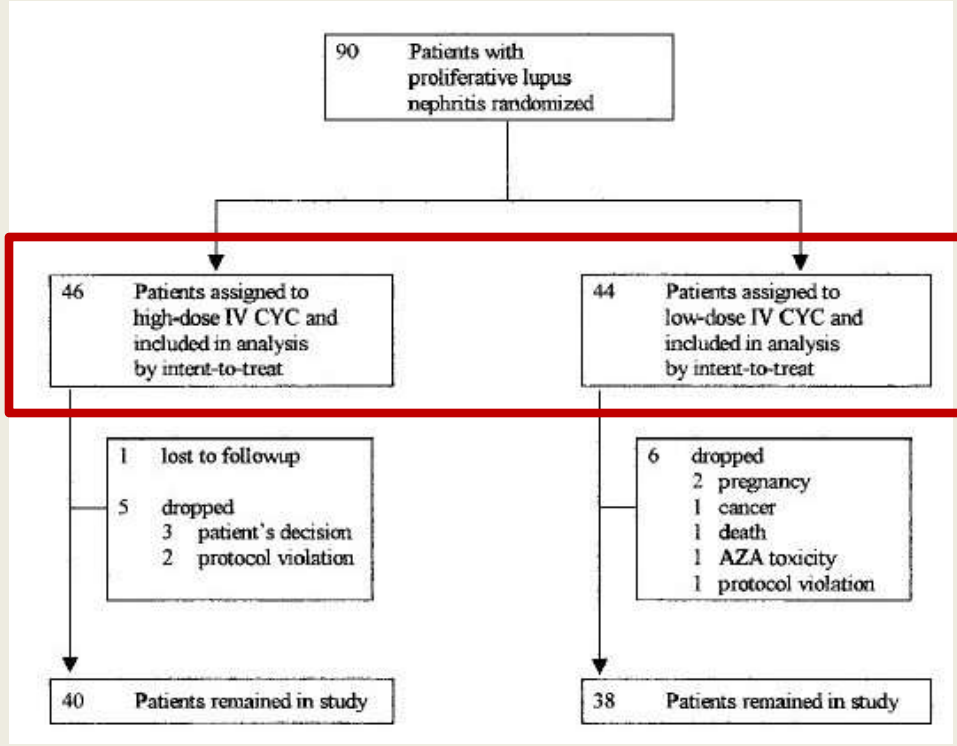
(B) Euro-Lupus Regimen

Immunosuppressive Therapy in Lupus Nephritis

The Euro-Lupus Nephritis Trial, a Randomized Trial of Low-Dose Versus High-Dose Intravenous Cyclophosphamide

Arthritis & Rheumatism

American College of Rheumatology
Education · Treatment · Research



Houssiau FA et al. Arthritis Rheum 2002; 46: 2121–2131

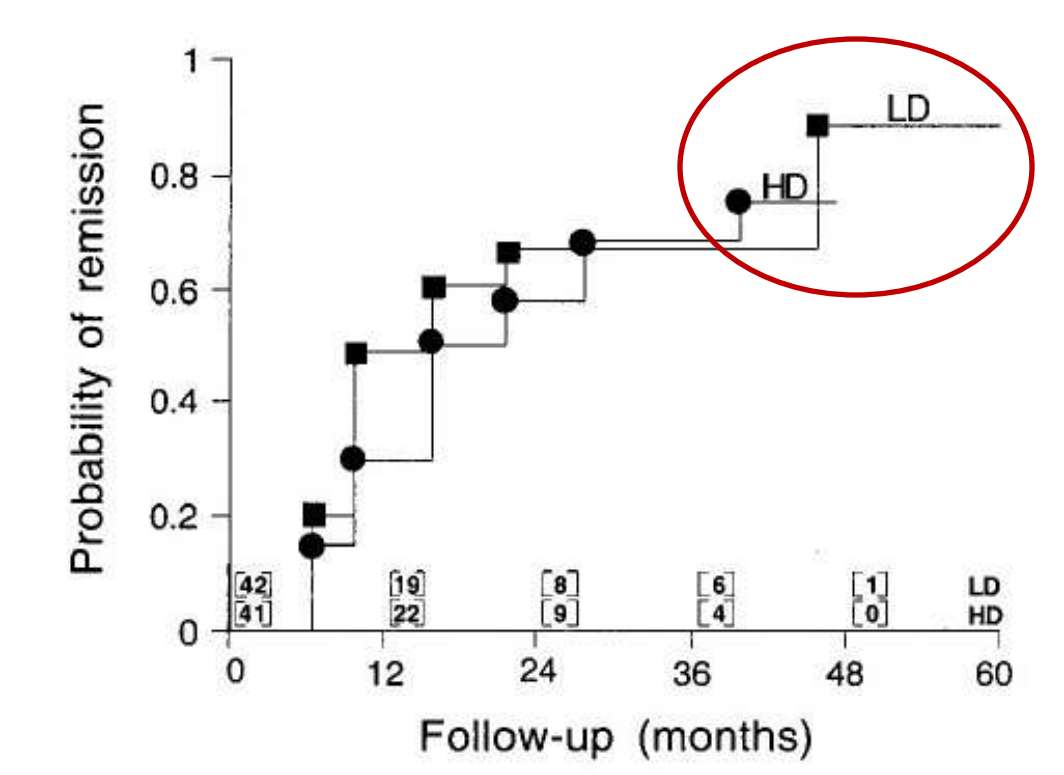
(B) Euro-Lupus Regimen

Immunosuppressive Therapy in Lupus Nephritis

The Euro-Lupus Nephritis Trial, a Randomized Trial of Low-Dose Versus High-Dose Intravenous Cyclophosphamide

Arthritis & Rheumatism

American College of Rheumatology
Education · Treatment · Research

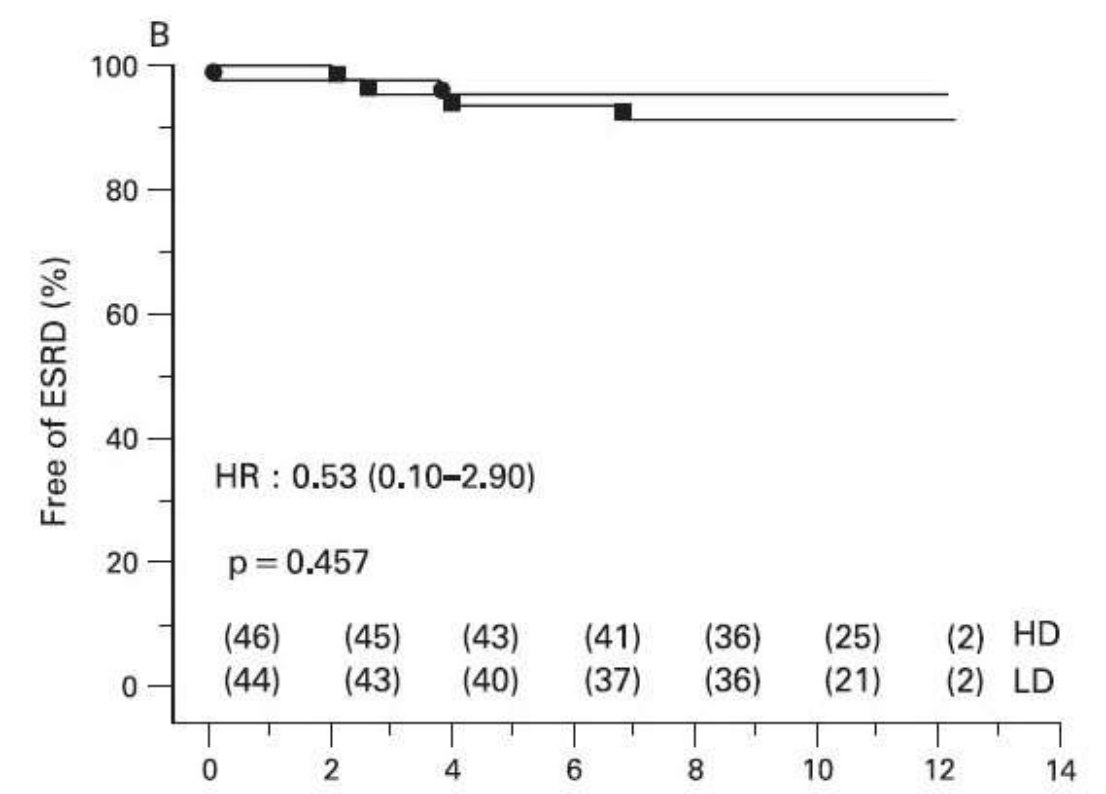


Houssiau FA et al. Arthritis Rheum 2002; 46: 2121–2131

(B) Euro-Lupus Regimen

The 10-year follow-up data of the Euro-Lupus Nephritis Trial comparing low-dose and high-dose intravenous cyclophosphamide

Annals of the RHEUMATIC DISEASES The EULAR Journal



Houssiau FA et al. Ann Rheum Dis 2010; 69: 61–64

Low Dose CYC: Egyptian Experience

Int Urol Nephrol
DOI 10.1007/s11255-007-9325-4

ORIGINAL ARTICLE

A comparative study of two intensified pulse cyclophosphamide remission-inducing regimens for diffuse proliferative lupus nephritis: an Egyptian experience

Alaa Sabry · Hamdy Abo-Zenah · Tarek Medhat · Hussein Sheashaa · Khaled Mahmoud · Amr El-Husceini

Conclusion A remission-inducing regimen of LD-CYC (cumulative dose 3 g) followed by AZA for SLE patients with proliferative LN achieves clinical results comparable to those obtained with HD-CYC without serious infection in both regimens.

Initial Therapy - Class III & IV
NIH vs Euro-Lupus

Table 28 | Regimens for initial therapy in class III/class IV LN

Regimen	A. NIH	B. Euro-Lupus	C. Oral cyclophosphamide	D. MMF
Cyclophosphamide	i.v. cyclophosphamide 0.5–1 g/m^2; monthly for 6 months	i.v. cyclophosphamide 500 mg; every 2 weeks for 3 months	Oral cyclophosphamide 1.0–1.5 mg/kg/d (maximum dose 150 mg/d) for 2–4 months	—
MMF	—	—	—	MMF up to 3 g/d for 6 months
Benefit shown by RCT in proliferative LN	Yes	Yes	Yes	Yes
Benefit shown by RCT in severe proliferative LN	Yes	Untested	Untested	Untested
Comments	Effective in whites, blacks, Hispanics, Chinese	Effective in whites. Untested in blacks, Hispanics, Chinese	Effective in whites, blacks, Chinese; easy to administer and lower cost than i.v. cyclophosphamide	Effective in whites, blacks, Hispanics, Chinese; high cost

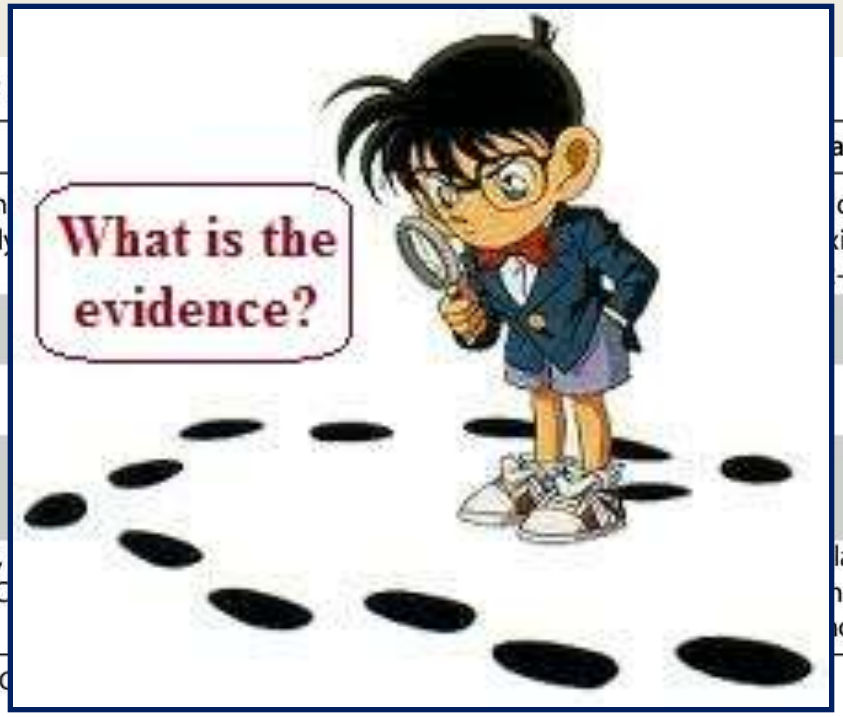
LN, lupus nephritis; MMF, mycophenolate mofetil; RCT, randomized controlled trial.
All regimens include corticosteroids:

- Oral prednisone, initial dose up to 0.5–1 mg/kg/d, tapering over 6–12 months according to clinical response.
- i.v. methylprednisolone is sometimes added initially for severe disease.

(C) MMF Regimen

Table 28 | Regimens for initial therapy

Regimen	A. NIH	amide	D. MMF
Cyclophosphamide	i.v. cyclophospham 0.5–1 g/m^2; monthly for 6 months	de ximum –4 months	—
MMF	—		MMF up to 3 g/d for 6 months
Benefit shown by RCT in proliferative LN	Yes		Yes
Benefit shown by RCT in severe proliferative LN	Yes		Untested
Comments	Effective in whites, blacks, Hispanics, C	lacks, Chinese; nd lower osphamide	Effective in whites blacks, Hispanics, Chinese; high cost



LN, lupus nephritis; MMF, mycophenolate mofetil; RC
All regimens include corticosteroids:

- Oral prednisone, initial dose up to 0.5–1 mg/kg/d, tapering over 6–12 months according to clinical response.
- i.v. methylprednisolone is sometimes added initially for severe disease.

(C) Mycophenolate Regimen vs IV CYC

Mycophenolate Mofetil *versus* Cyclophosphamide for Induction Treatment of Lupus Nephritis

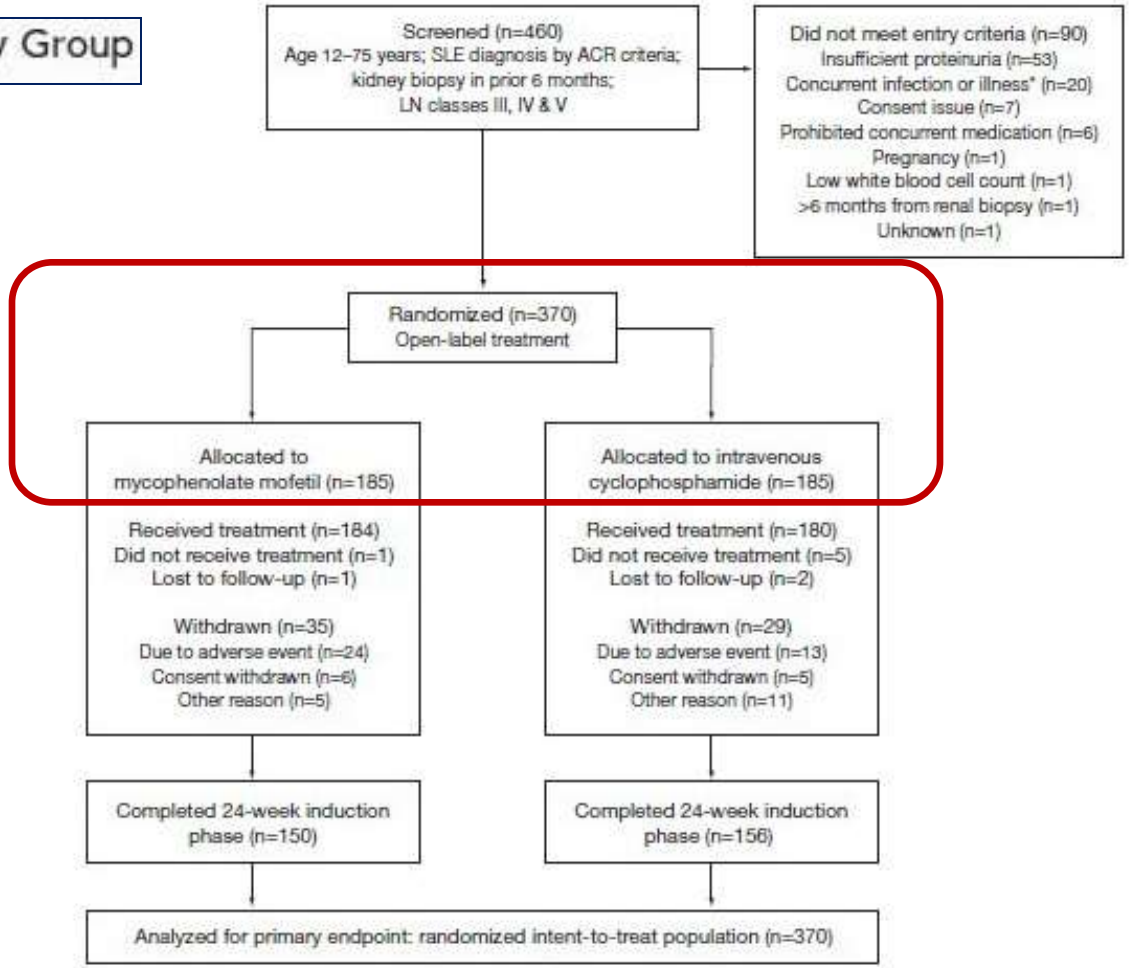
Aspreva Lupus Management Study Group

ALMS Trial

JASN®

370 patients with class III, IV, and V LN

Randomized to IV CYC pulses for 6 months or MMF 3gm/d target dose for 6 months



Appel GB et al. J Am Soc Nephrol 2009; 20: 1103–1112

(D) Mycophenolate Regimen vs IV CTX

Mycophenolate Mofetil *versus* Cyclophosphamide for Induction Treatment of Lupus Nephritis

Aspreva Lupus Management Study Group

ALMS Trial

JASN®

MMF had an equivalent response rate to i.v. cyclophosphamide at 6 months

Table 3. Summary of results of secondary efficacy end points[a]

Parameter	MMF (n = 185)	IVC (n = 185)	Odds Ratio (95% CI)
Responders with renal biopsy class III or IV	88 (56.4)[b]	83 (53.9)[c]	1.1 (0.7 to 1.8)
Patients with renal biopsy class V	16 (55.2)[d]	15 (48.4)[e]	
Renal remission criterion met			Treatment difference (% [95% CI])
serum creatinine	130 (70.3)	125 (67.6)	2.7 (−6.7 to 12.1)
urine protein	44 (23.8)	50 (27.0)	−3.2 (−12.1 to 5.6)
urine sediment	58 (31.4)	44 (23.8)	7.6 (−1.5 to 16.6)
all three criteria	16 (8.6)	15 (8.1)	0.5 (−5.1 to 6.2)
Renal and extrarenal remission			
complete absence of BILAG As and Bs	54 (29.7)[f]	45 (24.9)[g]	4.8 (4.3 to 14.0)
SELENA-SLEDAI			Difference between means (95% CI)
change in score from baseline to end point (mean ± SD)	−6.2 ± 10.1[h]	−6.6 ± 8.0[i]	0.41 (−1.48 to 2.30)
Anti-dsDNA			
patients with dsDNA >60 IU/ml at baseline[j]	117 (67.2)[k]	124 (72.5)[l]	
patients with dsDNA >60 IU/ml at end point	72 (41.4)[k]	91 (53.2)[l]	
C3			
patients with low C3 at baseline[m]	125 (71.0)[n]	139 (79.9)[k]	
patients with low C3 at end point[m]	70 (39.8)[n]	90 (51.7)[k]	
C4			
patients with low C4 at baseline[o]	104 (59.1)[n]	125 (72.3)[p]	
patients with low C4 at end point[o]	51 (29.0)[n]	72 (41.6)[p]	

[a]Data are n (%), unless specified otherwise. BILAG, British Isles Lupus Assessment Group Scale; SELENA-SLEDAI, Safety of Exogenous Estrogens in Lupus Erythematosus National Assessment / Systemic Lupus Erythematosus Disease Activity Index.

Appel GB et al. J Am Soc Nephrol 2009; 20: 1103–1112

(D) Mycophenolate Regimen vs IV CTX

Mycophenolate Mofetil *versus* Cyclophosphamide for Induction Treatment of Lupus Nephritis

Aspreva Lupus Management Study Group

ALMS Trial

JASN®

Similar incidence of adverse events including serious infections and deaths.

Table 4. Incidences of adverse events reported by >10% of patients[a]

Parameter	Patients Who Experienced at Least One AE	
	MMF (n = 184)	IVC (n = 180)
Deaths	9 (4.9)	5 (2.8)
Withdrawals as a result of AEs	24 (13.0)	13 (7.2)
All AEs	177 (96.2)	171 (95.0)
diarrhea	52 (28.3)	23 (12.8)
headache	38 (20.7)	47 (26.1)
peripheral edema	35 (19.0)	30 (16.7)
arthralgia	29 (15.8)	43 (23.9)
nausea	27 (14.7)	82 (45.6)
hypertension	26 (14.1)	25 (13.9)
nasopharyngitis	25 (13.6)	29 (16.1)
vomiting	25 (13.6)	68 (37.8)
cough	24 (13.0)	16 (8.9)
anemia	23 (12.5)	12 (6.7)
alopecia	20 (10.9)	64 (35.6)
abdominal pain	19 (10.3)	13 (7.2)
back pain	19 (10.3)	16 (8.9)
muscle spasms	19 (10.3)	17 (9.4)
rash	19 (10.3)	21 (11.7)
urinary tract infection	19 (10.3)	17 (9.4)

Appel GB et al. J Am Soc Nephrol 2009; 20: 1103–1112

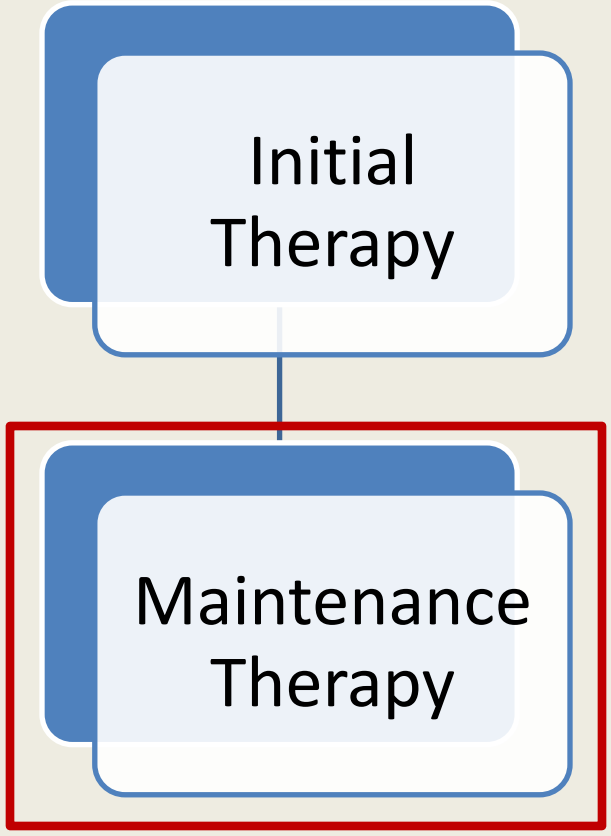
Class III & IV Management Overview

The evolution of initial therapy in proliferative LN has been to reduce toxicity while maintaining efficacy.

The objective is to rapidly decrease kidney inflammation by initial intensive treatment,

and then

consolidate treatment over a longer time.



At the end of initial therapy, remission may not be achieved.

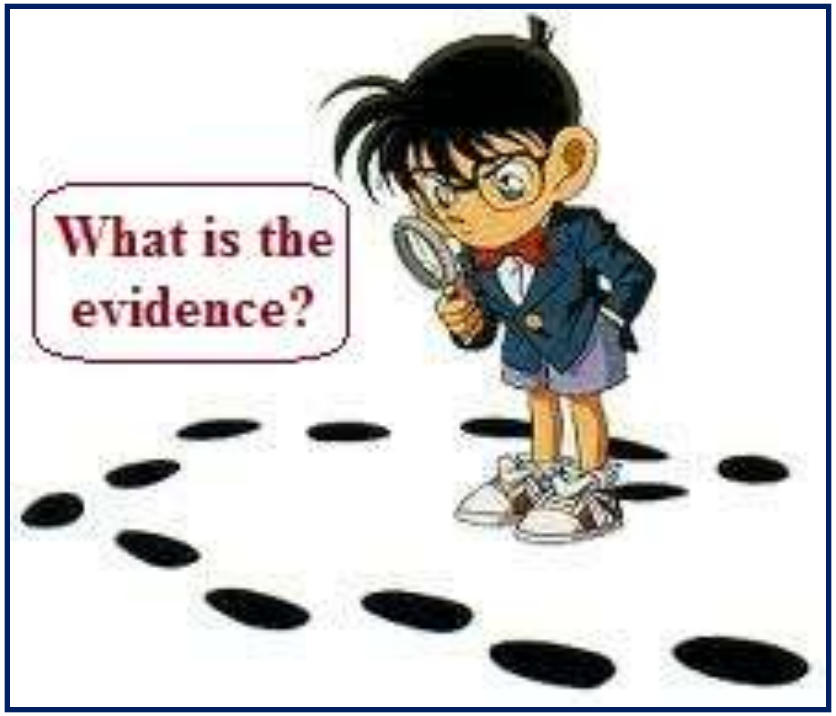
Remissions continue to occur well into the maintenance phase.

Class III and Class IV Lupus Nephritis (A & A/C) management

Maintenance Therapy

Recommend low-dose oral corticosteroids (≤10 mg/d predsniolone equivelant) (1B)

with



Choice of Maintenance Therapy
Class III & IV - MMF vs AZA

Annals of the RHEUMATIC DISEASES The EULAR Journal

Azathioprine versus mycophenolate mofetil for long-term immunosuppression in lupus nephritis: results from the MAINTAIN Nephritis Trial

Compared MMF with AZA as maintenance therapy in a predominantly Caucasian population after initial treatment with low-dose cyclophosphamide.

The primary end-point was time to kidney relapse.

Houssiau FA et al. Ann Rheum Dis 2010; 69: 2083–2089.

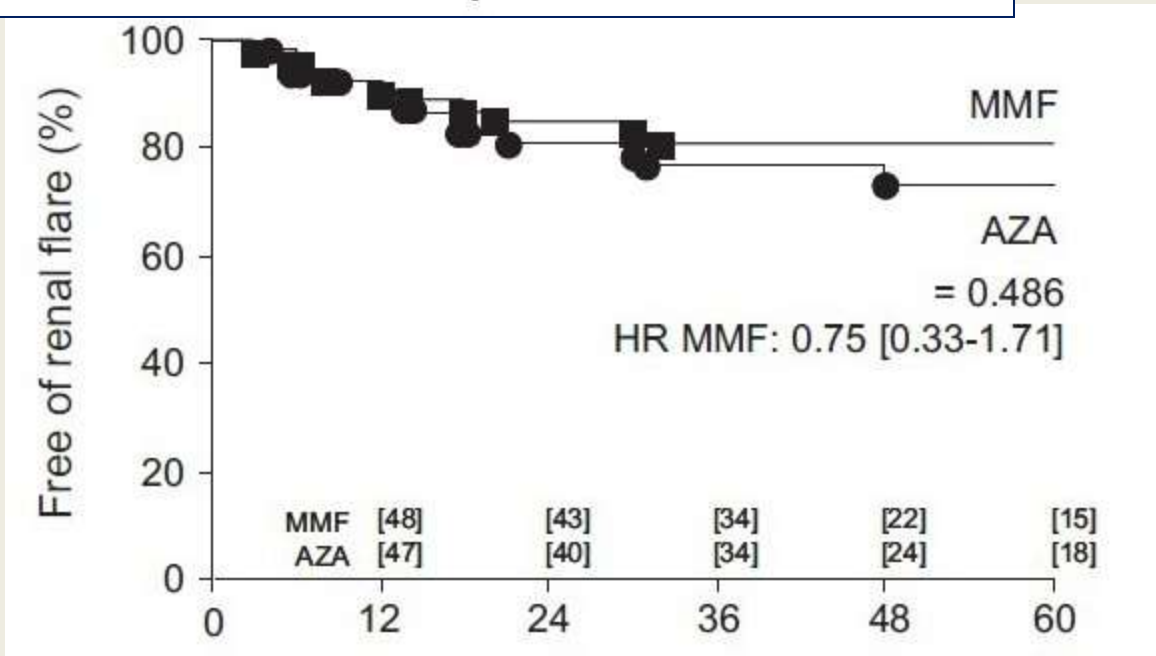
Choice of Maintenance Therapy

Class III & IV - MMF vs AZA

Annals of the RHEUMATIC DISEASES The EULAR Journal

Azathioprine versus mycophenolate mofetil for long-term immunosuppression in lupus nephritis: results from the MAINTAIN Nephritis Trial

After at least 3 years of follow-up, this trial found MMF and azathioprine to be equivalent.



Houssiau FA et al. Ann Rheum Dis 2010; 69: 2083–2089.

Choice of Maintenance Therapy
Class III & IV - MMF vs AZA

The NEW ENGLAND JOURNAL of MEDICINE

Mycophenolate versus Azathioprine as Maintenance Therapy for Lupus Nephritis

Mary Anne Dooley, M.D., M.P.H., David Jayne, M.D., Ellen M. Ginzler, M.D., M.P.H., David Isenberg, M.D., Nancy J. Olsen, M.D., David Wofsy, M.D., Frank Eitner, M.D., Gerald B. Appel, M.D., Gabriel Contreras, M.D., M.P.H., Laura Lisk, B.Sc., and Neil Solomons, M.D., for the ALMS Group*

ALMS trial extension phase.

Compared MMF and AZA as maintenance therapies after the 6-month initial treatment period .

Patients entered this extension phase only if they achieved a complete or partial remission after initial therapy.

Dooley et al. N Engl J Med 2011; 365: 1886–1895.

Choice of Maintenance Therapy

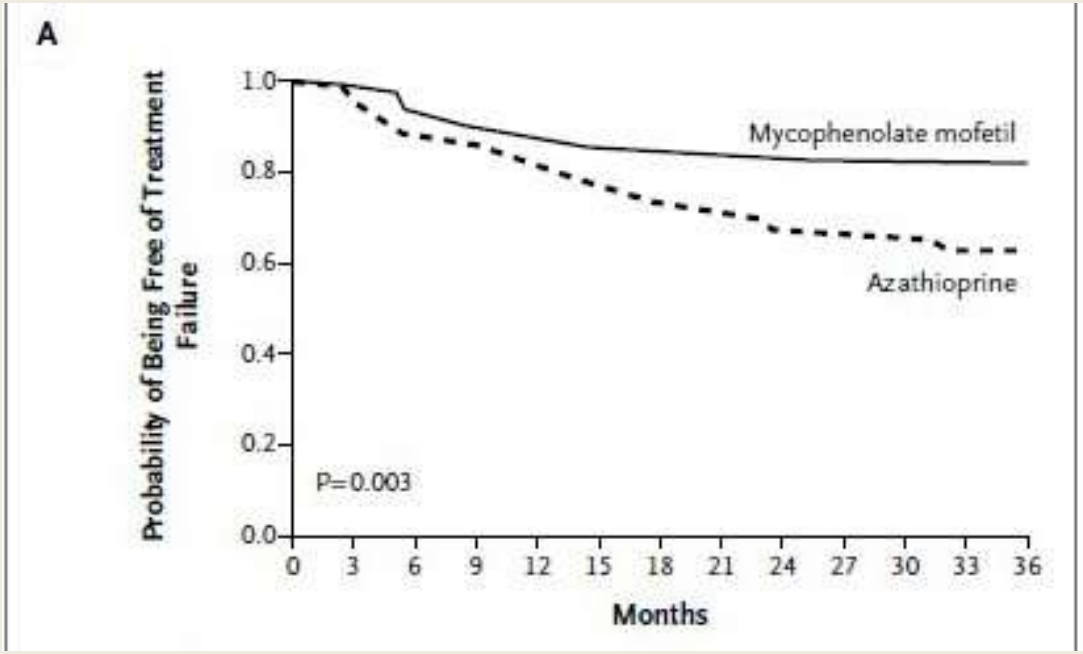
Class III & IV - MMF vs AZA

The NEW ENGLAND JOURNAL of MEDICINE

Mycophenolate versus Azathioprine as Maintenance Therapy for Lupus Nephritis

Mary Anne Dooley, M.D., M.P.H., David Jayne, M.D., Ellen M. Ginzler, M.D., M.P.H., David Isenberg, M.D., Nancy J. Olsen, M.D., David Wofsy, M.D., Frank Eitner, M.D., Gerald B. Appel, M.D., Gabriel Contreras, M.D., M.P.H., Laura Lisk, B.Sc., and Neil Solomons, M.D., for the ALMS Group*

Over 3 years, the composite treatment failure end-point (death, ESRD, kidney flare, sustained doubling of SCr, or requirement for rescue therapy) was reached in 16% of MMF-treated patients compared to 32% of azathioprine-treated patients.



Dooley et al. N Engl J Med 2011; 365: 1886–1895.

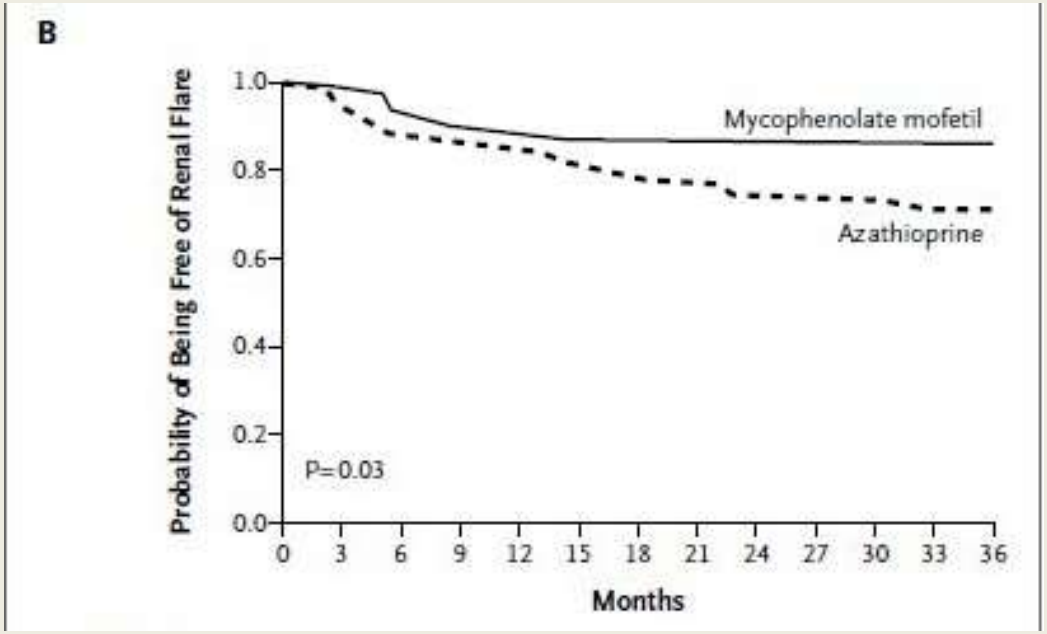
Choice of Maintenance Therapy
Class III & IV - MMF vs AZA

The NEW ENGLAND JOURNAL of MEDICINE

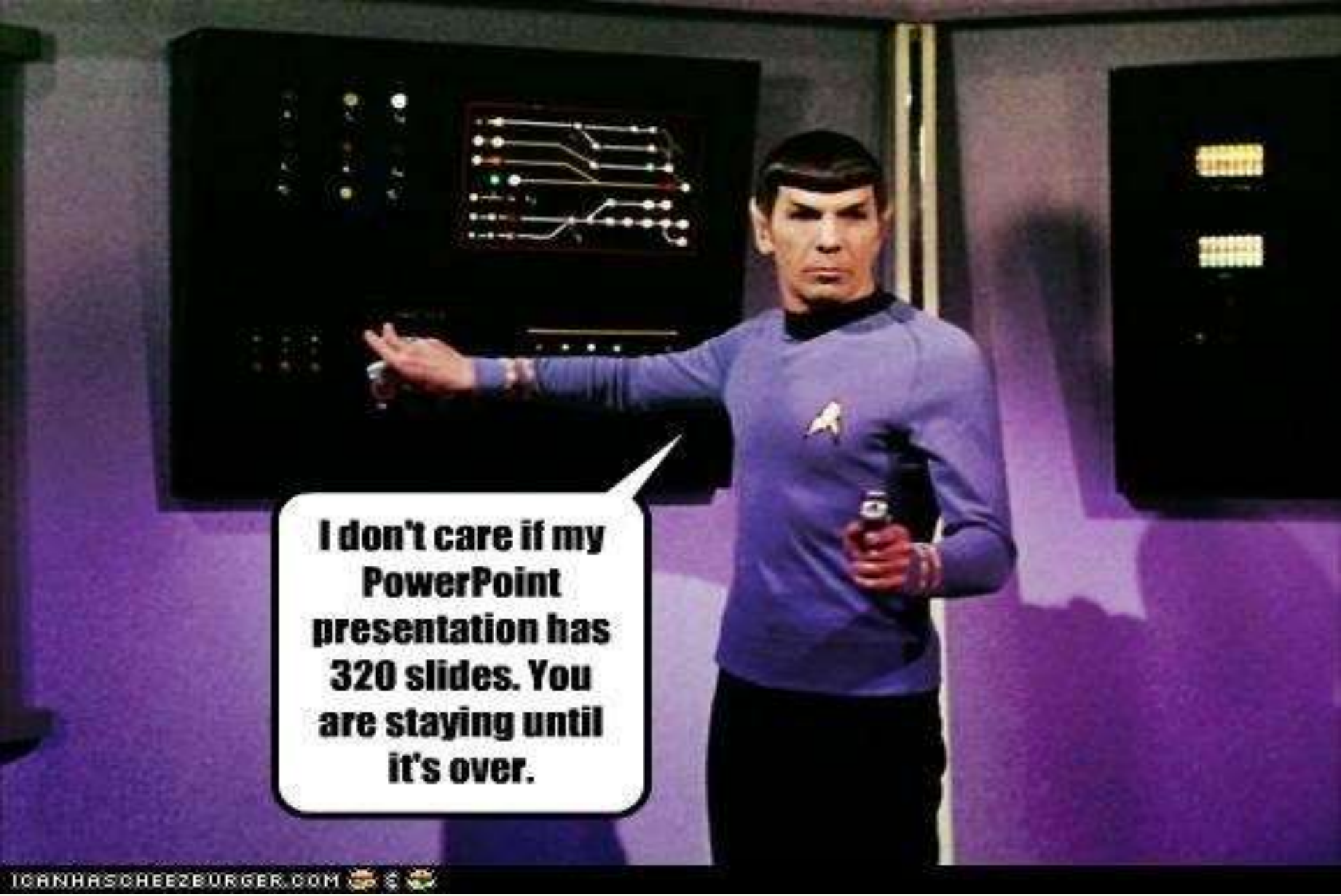
Mycophenolate versus Azathioprine as Maintenance Therapy for Lupus Nephritis

Mary Anne Dooley, M.D., M.P.H., David Jayne, M.D., Ellen M. Ginzler, M.D., M.P.H., David Isenberg, M.D., Nancy J. Olsen, M.D., David Wofsy, M.D., Frank Eitner, M.D., Gerald B. Appel, M.D., Gabriel Contreras, M.D., M.P.H., Laura Lisk, B.Sc., and Neil Solomons, M.D., for the ALMS Group*

Over 3 years, the composite treatment failure end-point (death, ESRD, kidney flare, sustained doubling of SCr, or requirement for rescue therapy) was reached in 16% of MMF-treated patients compared to 32% of azathioprine-treated patients.



Dooley et al. N Engl J Med 2011; 365: 1886–1895.

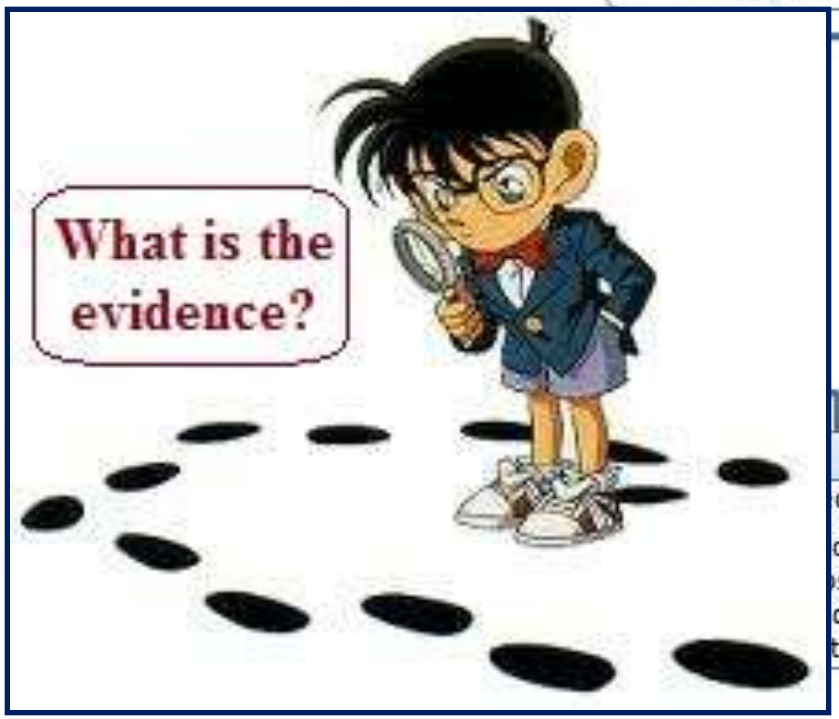

I don't care if my PowerPoint presentation has 320 slides. You are staying until it's over.
ICANHASCHEEZBURGER.COM

Class V Lupus Nephritis management

Check:

1- Kidney function

2- Proteinuria range



commend

costeroids &

suppressives as

d by extrarenal

tions of lupus (2D)

There are no convincing data to treat class V LN and subnephrotic proteinuria with immunosuppression; however, given the adverse effects of proteinuria on the kidney, it is reasonable to treat these patients with antiproteinuric and antihypertensive medications

Class V – Nephrotic Range
Cyclosporine vs CYC

Randomized, Controlled Trial of Prednisone, Cyclophosphamide, and Cyclosporine in Lupus Membranous Nephropathy

JASN®

Characteristics	Prednisone Group 1	IVCY Group 2	CsA Group 3
Gender (female/male)	12/3	12/3	11/1
Age (yr; median [range])	40 (20 to 58)	41 (17 to 60)	34 (13 to 56)
Race/ethnicity (white/other)[a]	3/12	8/7	1/11
Duration of LMN before study entry (mo; median [range])	11.5 (3 to 120)	7 (2 to 24)	6 (1 to 16)
GFR (ml/min per 1.73 m^2; median [range])	80 (32 to 112)	80 (61 to 112)	89 (68 to 189)
Proteinuria (g/d; median [range])	5.7 (2.8 to 10.6)	5.0 (2.7 to 15.4)	5.8 (2.7 to 13.8)
Serum albumin (g/dl; median [range])	2.7 (1.3 to 3.6)	3.0 (1.6 to 3.6)	2.5 (1.9 to 3.3)
Cholesterol (mg/dl; median [range])	297 (207 to 501)	268 (173 to 339)	279 (194 to 631)
Hematocrit (%; median [range])	36 (31 to 45)	38 (33 to 45)	36 (27 to 42)
Anti dsDNA antibodies (patients)	4	3	2
Low C3 complement (patients)	1	1	1
Low C4 complement (patients)	2	0	1

[a] White refers to non–Hispanic white patients, and other refers to black and Hispanic patients.

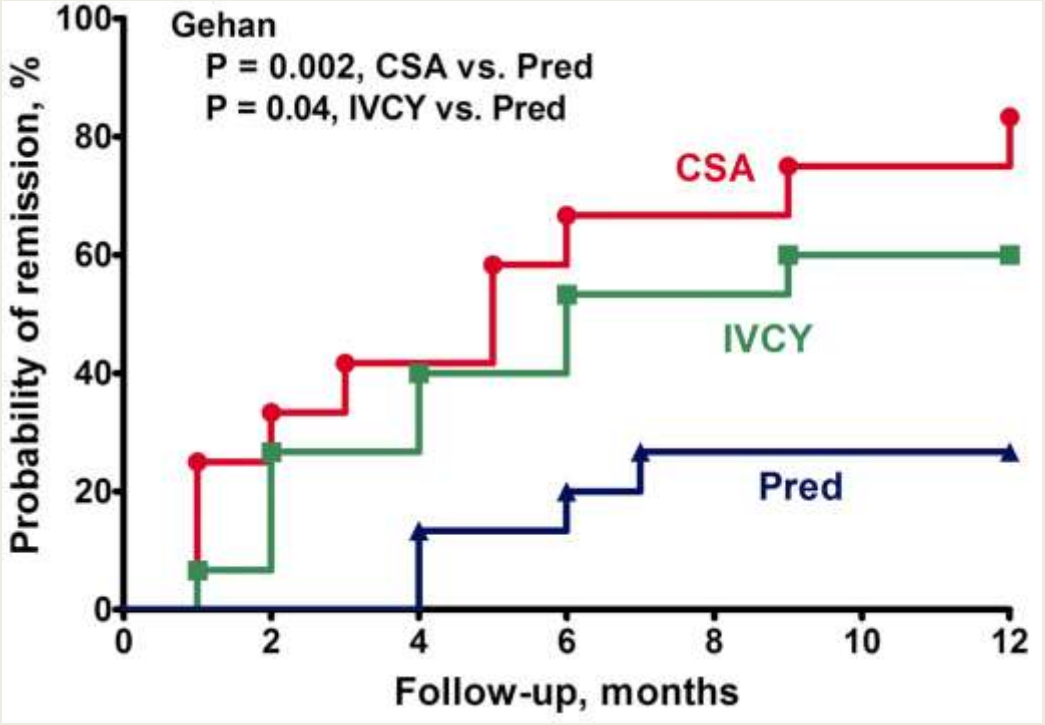
Austin III HA et al. J Am Soc Nephrol 2009; 20: 901–911.

Class V – Nephrotic Range
Cyclosporine vs CYC

Randomized, Controlled Trial of Prednisone, Cyclophosphamide, and Cyclosporine in Lupus Membranous Nephropathy

JASN®

Both cyclophosphamide and cyclosporine significantly increased response



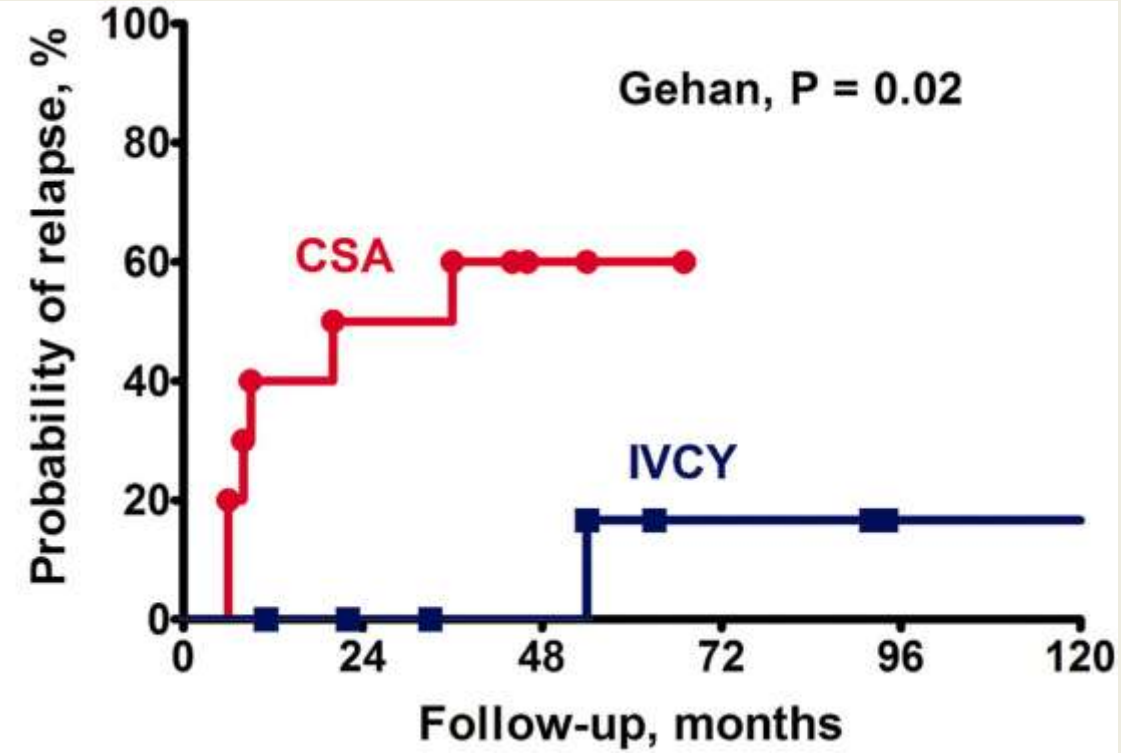
Austin III HA et al. J Am Soc Nephrol 2009; 20: 901–911.

Class V – Nephrotic Range
Cyclosporine vs CYC

Randomized, Controlled Trial of Prednisone, Cyclophosphamide, and Cyclosporine in Lupus Membranous Nephropathy

JASN®

Relapse after stopping therapy was much more likely in those treated with cyclosporine compared to cyclophosphamide (no relapse in 48 months).



Austin III HA et al. J Am Soc Nephrol 2009; 20: 901–911.

Lupus Nephritis ISN/RPS Classification

Class I	**Minimal mesangial lupus nephritis**
	Normal glomeruli by light microscopy, but mesangial immune deposits by immunofluorescence
Class II	**Mesangial proliferative lupus nephritis**
	Purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microsocpy, with mesangial immune deposits
	A few isolated subepithelial or subendothelial deposits may be visible by immunofluorescence or electron microscopy, but not by light microscopy
Class III	**Focal lupus nephritis[a]**
	Active or inactive focal, segmental or global endo- or extracapillary glomerulonephritis involving <50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations
Class III (A)	Active lesions: focal proliferative lupus nephritis
Class III (A/C)	Active and chronic lesions: focal proliferative and sclerosing lupus nephritis
Class III (C)	Chronic inactive lesions with glomerular scars: focal sclerosing lupus nephritis
Class IV	**Diffuse lupus nephritis[b]**
	Active or inactive diffuse, segmental or global endo- or extracapillary glomerulonephritis involving ≥50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class is divided into diffuse segmental (IV-S) lupus nephritis when ≥50% of the involved glomeruli have segmental lesions, and diffuse global (IV-G) lupus nephritis when ≥50% of the involved glomeruli have global lesions. Segmental is defined as a glomerular lesion that involves less than half of the glomerular tuft. This class includes cases with diffuse wire loop deposits but with little or no glomerular proliferation.
Class IV-S (A)	Active lesions: diffuse segmental proliferative lupus nephritis
Class IV-G (A)	Active lesions: diffuse global proliferative lupus nephritis
Class IV-S (A/C)	Active and chronic lesions: diffuse segmental proliferative and sclerosing lupus nephritis
Class IV-G (A/C)	Active and chronic lesions: diffuse global proliferative and sclerosing lupus nephritis
Class IV-S (C)	Chronic inactive lesions with scars: diffuse segmental sclerosing lupus nephritis
Class IV-G (C)	Chronic inactive lesions with scars: diffuse global sclerosing lupus nephritis
Class V	**Membranous lupus nephritis**
	Global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations
	Class V lupus nephritis may occur in combination with class III or IV in which case both will be diagnosed
	Class V lupus nephritis may show advanced sclerosis
Class VI	**Advanced sclerotic lupus nephritis**
	≥90% of glomeruli globally sclerosed without residual activity

Indicate and grade (mild, moderate, severe) tubular atrophy, interstitial inflammation and fibrosis, severity of arteriosclerosis or other vascular lesions.

[a] Indicate the proportion of glomeruli with active and with sclerotic lesions.

[b] Indicate the proportion of glomeruli with fibrinoid necrosis and/or cellular crescents.

12.7: Class VI LN (advanced sclerosis LN)

12.7.1: We recommend that patients with class VI LN be treated with corticosteroids and immunosuppressives only as dictated by the extrarenal manifestations of systemic lupus. (*2D*)

The Road Map

Histopathology of Lupus Nephritis

Conventional Therapies

Future Therapy

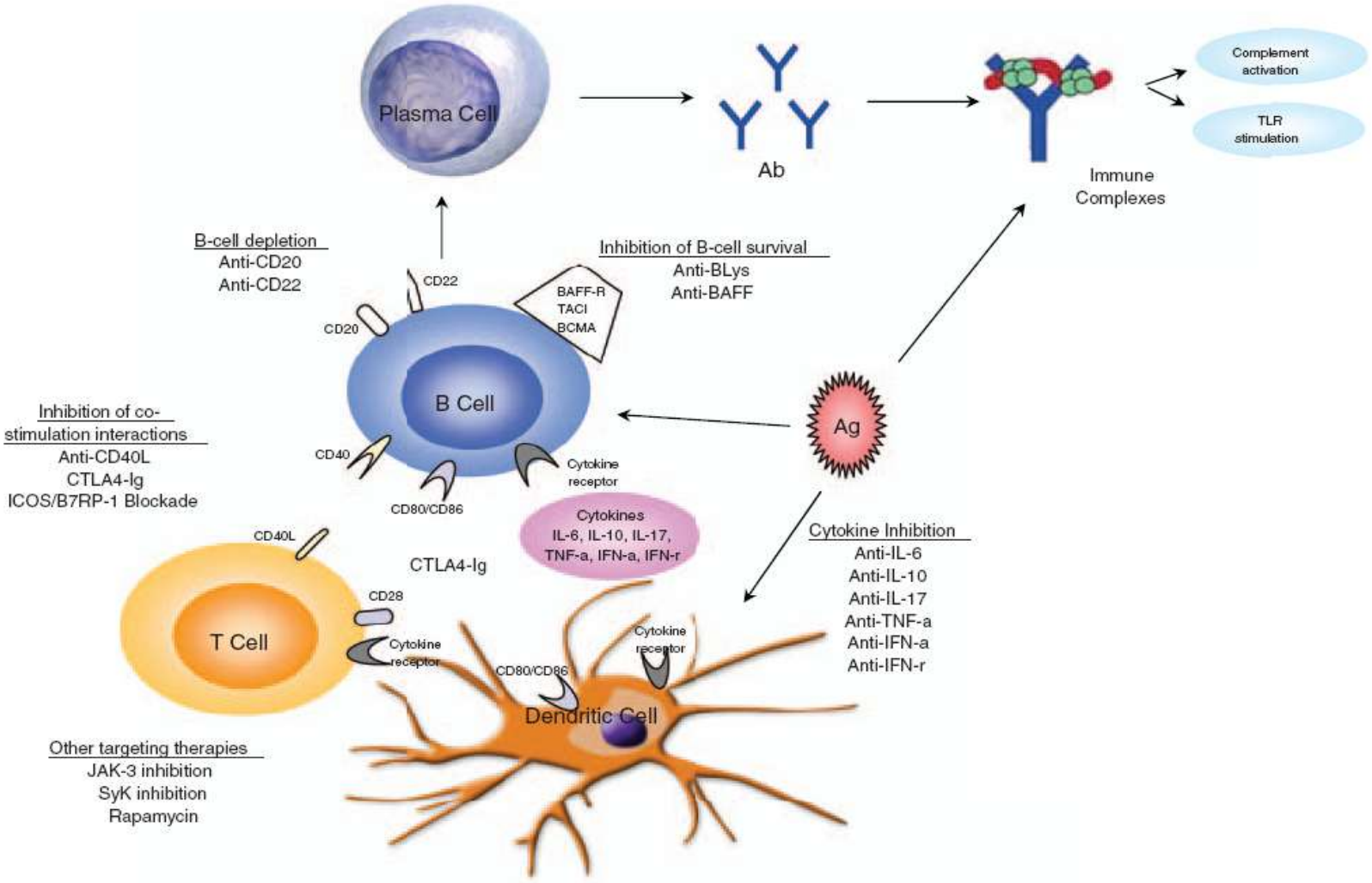


Figure. 1. Mechanism of target biological therapies in SLE. Ag: antigen; Ab: antibody; Anti-IL-6: anti-interleukin-6; Anti-IL-10: anti-interleukin-10; Anti-IL-17: anti-interleukin-17; anti-TNF: anti-tumor necrosis factor; anti-IFN-a: anti-interferon-a; Anti-IFN-r: anti-interferon-r; TLR: toll like receptor; CTLA4-Ig: cytotoxic T lymphocyte activator 4-immunoglobulin; ICOS: Inducible co-stimulator; B7RP-1: B7-related protein-1; BAFF-R: B-cell activating factor; TACI: transmembrane activator and calcium-modulating cyclophilin ligand interactor; BCMA: B cell maturation antigen; SyK: Spleen tyrosine kinase. Adapted by the author and reprinted with permission from Klippel, J. H. *et al. Primer on the Rheumatic Diseases*. 13th ed. pp. 335.

Future Directions

Site of action	Agent	Study	Lupus nephritis	Others
1-B Cells	***RITUXIMAB(CD20)*** ***Ocrelizumab (CD20)*** ***Epratazumab(D22)***	**EXPLORER** **LUNAR** **BELONG** **EMBLEM trial**	**NO** **YES** **NO** **NO**	**unlike rituximab it is fully humanized (BELONG) was suspended prematurely due to an increased incidence of serious and opportunistic infections**
2-B growth factors (BLYs- BAFF)	**Belimumab**	**BLISS-52** **BLISS-76**	**NO** **NO**	**Benelysta® (Glaxosmithkline, Canada), was approved (March 2011) by the U.S. Food and Drug Administration for the treatment of mild to moderate SLE**
3-Plasma Cells	**Bortezomib**	**a clinical trial to test its efficacy is seeking to enroll patients**	**YES**	**ClinicalTrials.gov Identifier: NCT01169857**
4-Targeting Co-stimulatory Molecule This molecule binds to B7 on the APC, blocking the co-stimulatory signal needed for cell activation.	**Abatacept**	**Bristol-Myers Squibb** **National Institute of Allergy and Infectious Diseases**	**YES** **YES**	**ClinicalTrials.gov Identifier: NCT00430677** **ClinicalTrials.gov Identifier: NCT00774852**
5-C5 COMPONENT OF THE COMPLEMENT SYSTEM	**Eculizumab**	phase I study	**NO**	significant clinical improvement in SLE symptoms was not stated during assessments **March 2007 FDA PNH**
6-CD40L		**Open label (28 paatients with Proliferative nephritis** **Randomied study**	**YES** **No**	Boumpas (2003) *Arthritis Rheum.*, ***48(3), 719-*** 727 **Stopped prematurely due to thromboembolic events**
7-anti-dsDNA antibodies.	**Abetimus sodium**	Randomied controlled phase iii (Alarcón-Segovia D. *Arthritis Rheum 2003; 48: 442-54.* ASPEN(Cardiel MH *Arthritis Rheum 2008; 58: 2470-80*	**YES**	**Failed to prolong time to renal flare**

Future Directions

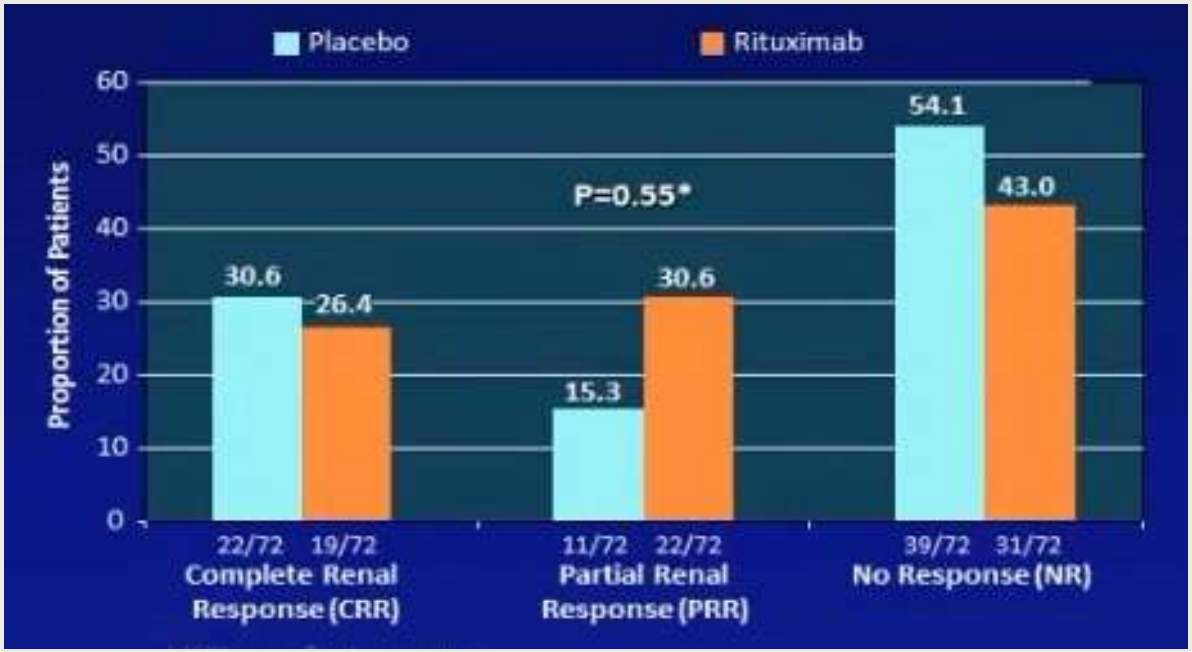
Site of action	Agent	Study	Lupus nephritis	Others
8-Cytokine inhibitors	Atacicept	A phase II study	YES	was terminated because of severe infections
12-Human recombinant IL-I receptor antagonist (anakinra, Kineret® Amgen, USA)		Two very small uncontrolled studies of three and four SLE patients Ostendorf B, *Ann Rheum Dis 2005; 64: 630-3.*	NO	might have beneficial effects on musculoskeletal lupus-related manifestations No current clinical trials
13-Anti-IL-6 receptor antibody (actemra, Tocilizumab®, Roche, Switzerland)	Tocilizumab	Illei GG, *Arthritis Rheum 2010; 62: 542-52.* open phase I trial	NO	2, 4, 8 mg/kg intravenously every other week for 12 weeks) in 16 lupus patients with mild to moderate disease activity Tocilizumab was significant Neutropenia in significant clinical improvement (≥ 4 SLENA-SLEDAI index points), especially in patients with arthritis
9-Interferon-alpha inhibition (anti-IFNα)	AMG 811	phase Ib, randomized, multicenter, dose-escalation study in approximately 40 SLE subjects with and without glomerulonephritis	YES	ClinicalTrials.gov identifier: NCT00818948
10-Peptide-based treatments	edratide	PRELUDE	NO	the trial failed to reach its primary outcome – namely, reduction of SLEDAI as compared to placebo
11-Tumor-necrosis factor alpha (TNFα)	Infliximam	Aringer M, *Arthritis Rheum 2004; 50: 3161-9.* Hayat (2007) *Clin. Rheumatol., 26(6), 973-975.* . [Aringer et al. 2009ClinicalTrials.gov identifiers: NCT00368264 and NCT00447265	YES YES	
14-Others	*Laquinimod*	reduce leukocyte infiltration into target tissues, alters the balance of Th1/Th2 lymphocytes	YES	ongoing trial NCT01085097

Does Rituximab have a role in initial therapy of proliferative LN?

Arthritis & Rheumatism

American College of Rheumatology
Education · Treatment · Research

Efficacy And Safety Of Rituximab In Subjects With Active Proliferative Lupus Nephritis (LN): Results From The Randomized, Double-Blind Phase III LUNAR Study



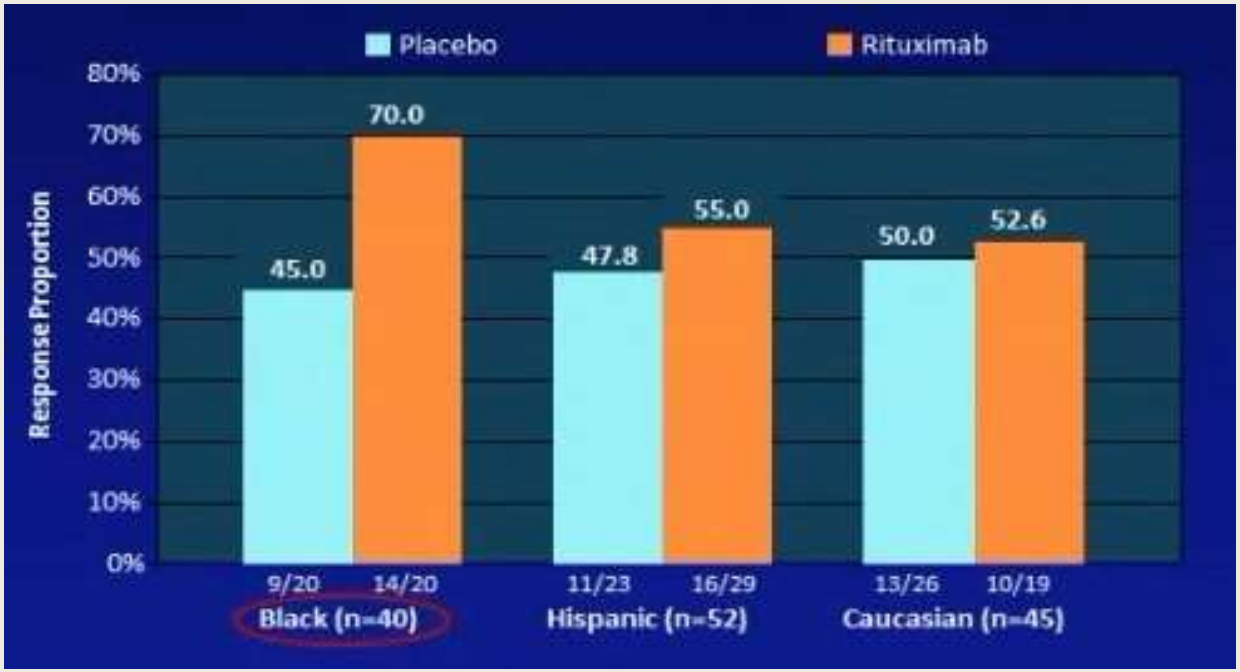
Rovin BH et al. J Am Soc Nephrol 2009; 20: 77A

Does Rituximab have a role in initial therapy of proliferative LN?

Arthritis & Rheumatism

American College of Rheumatology
Education · Treatment · Research

Efficacy And Safety Of Rituximab In Subjects With Active Proliferative Lupus Nephritis (LN): Results From The Randomized, Double-Blind Phase III LUNAR Study



Rovin BH et al. J Am Soc Nephrol 2009; 20: 77A.

Does Rituximab have a role in initial therapy of proliferative LN?

Arthritis & Rheumatism

American College of Rheumatology
Education · Treatment · Research

Efficacy And Safety Of Rituximab In Subjects With Active Proliferative Lupus Nephritis (LN): Results From The Randomized, Double-Blind Phase III LUNAR Study

Because the kidney response rate for class III and IV LN with any of the initial therapies so far discussed is only about 60% at 6–12 months, an RCT adding rituximab or placebo to MMF plus corticosteroids for initial LN therapy was undertaken to determine if remission rates could be improved.

At 12 months, there were no differences between the rituximab and placebo groups in terms of complete or partial remissions.

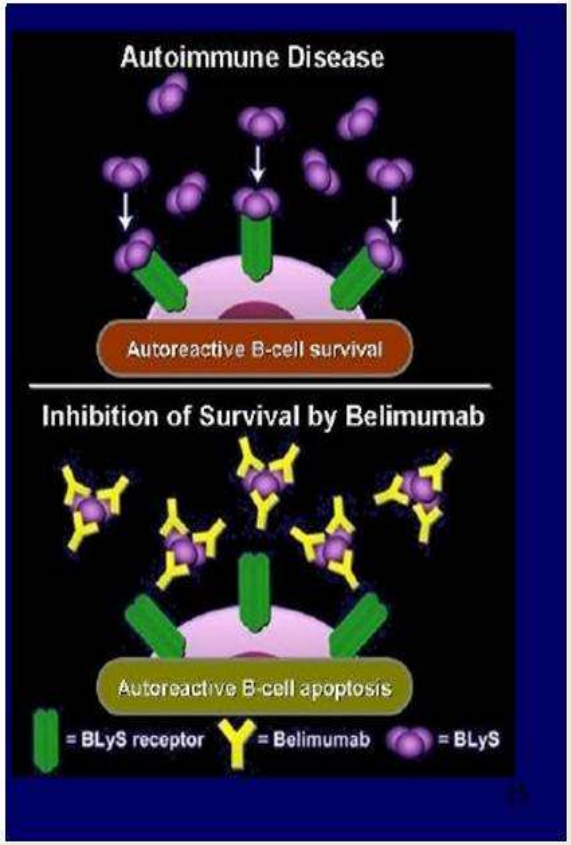
Neutropenia, leukopenia, and hypotension occurred more frequently in the rituximab group.

Thus, rituximab cannot be recommended as adjunctive initial therapy.

Rovin BH et al. J Am Soc Nephrol 2009; 20: 77A.

Future Directions

B)-Therapies Targeting B growth factors



B lymphocyte stimulator, also known as BAFF (a member of the tumor necrosis ligand superfamily), is a key factor in maturation and survival of B cells.

BLyS over-expression is a feature of SLE.

Patients with SLE appeared to have significantly high levels of circulating BLyS protein compared to controls.

Plasma BLyS levels appear to correlate with immunoglobulin G levels and anti-dsDNA autoantibody titers.

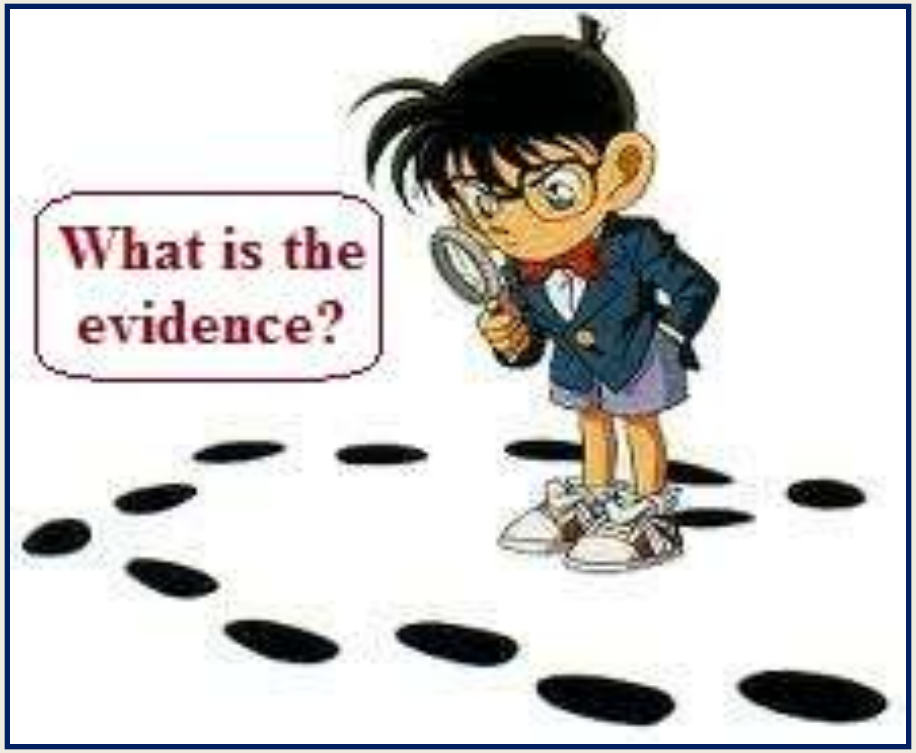
Higher BLyS levels were associated with disease activity, as defined by the SELENA-SLEDAI score

Thus, BLyS antagonism may be beneficial in the treatment of SLE.

[Vadacca et al. 2010].

Instead of targeting B cells directly, is a humanized monoclonal antibody that targets the B cell growth factor B lymphocyte stimulator protein (BLyS), also known as B cell activating factor (BAFF).

B)-Therapies Targeting B growth factors



Future Directions

B)-Therapies Targeting B growth factors

BLISS76

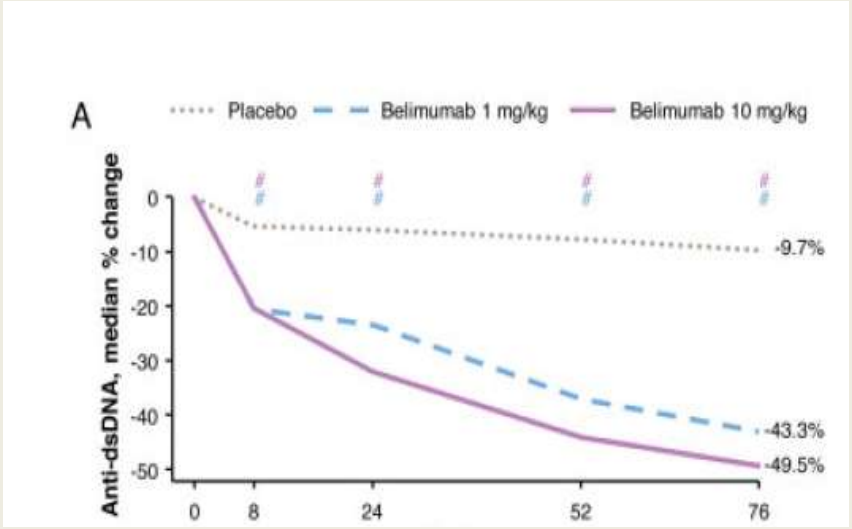
A Phase III, Randomized, Placebo-Controlled Study of Belimumab, a Monoclonal Antibody That Inhibits B Lymphocyte Stimulator, in Patients With Systemic Lupus Erythematosus

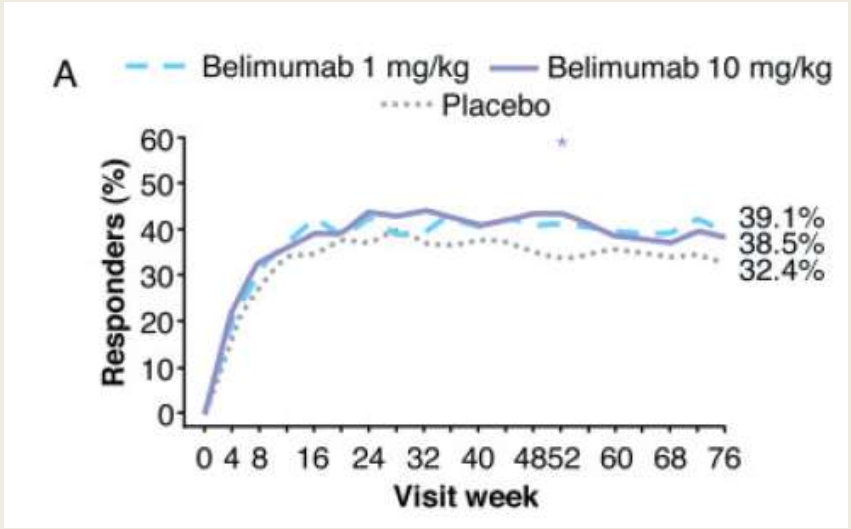
ARTHRITIS & RHEUMATISM
Vol. 63, No. 12, December 2011, pp 3918–3930

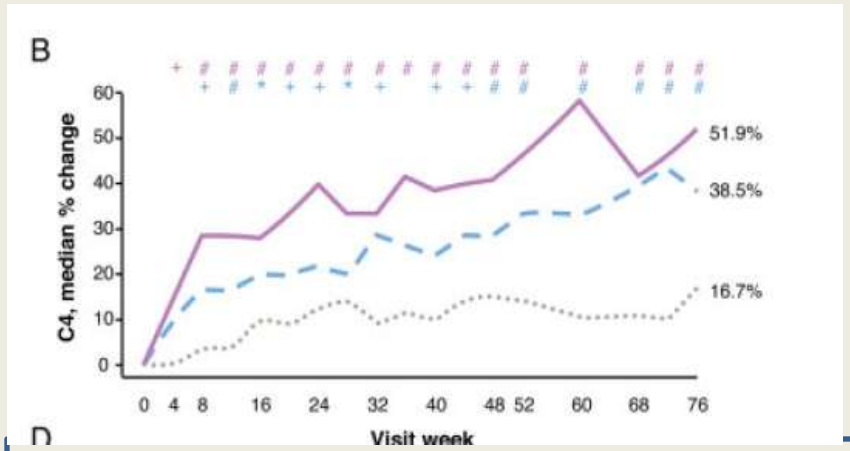
A 76-week, multinational (North America and Europe) study
A total of 819 patients were enrolled

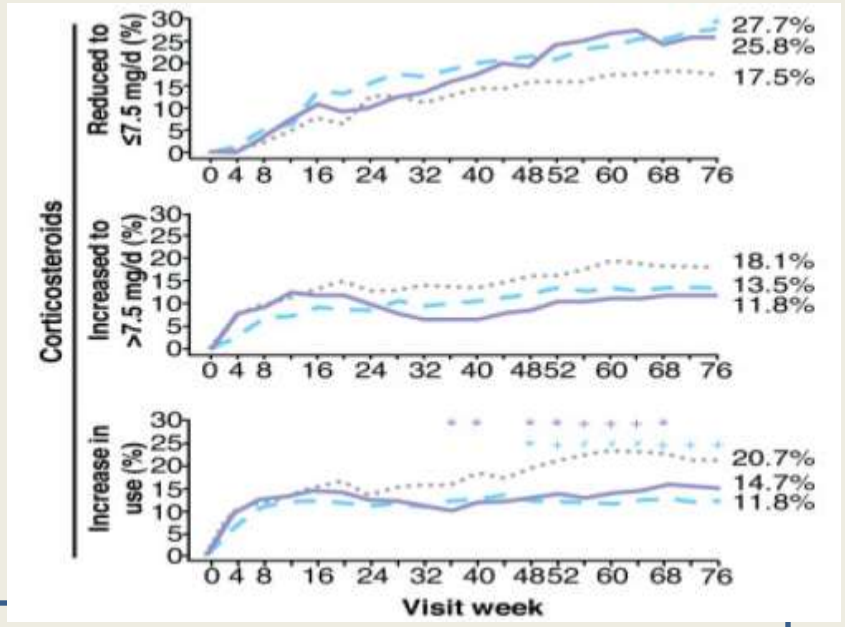
Belimumab or placebo was administered at weeks 0, 14, and 28, and then every 28 days to week 72, followed by an evaluation at week 76.
(271, 273, and 275 patients in the belimumab 1- and 10-mg/kg/dosegroups and the placebo group, respectively).

Overall, belimumab appeared more efficacious as measured using a number of parameters compared withplacebo in this 76-week, well-designed study.
There was no consistent dose-related effect of belimumab.









Richard Furie,et al . Arthritis &Rheumatism 63(12):2011;3918–3930

Future Directions
anti-TNFα **treatment**

ELSEVIER

CYTOKINE

www.elsevier.com/locate/issn/10434666

Cytokine 35 (2006) 148–153

Proinflammatory cytokines (TNF-α and IL-6) in Egyptian patients with SLE: Its correlation with disease activity

Alaa Sabry [a,*], Hussein sheashaa [a], Amr El-husseini [a], Khaleed Mahmoud [a], Khaleed F. Eldahshan [a], Shahir K. George [a], Ehab Abdel-Khalek [a], E.M. El-Shafey [b], Hamdy Abo-Zenah [c]

[a] *Nephrology and Internal medicine department, Mansoura Urology and Nephrology Center, Mansoura University, Egypt*
[b] *Internal Medicine, Nephrology department, Tanta University, Egypt*
[c] *Faculty of Medicine, Menufiya University, Egypt*

Received 20 July 2005; accepted 26 July 2006

between TNF-α and IL-6 serum levels and the SLEDAI score was observed ($r = .743$ and .772, respectively). *Conclusion:* Serum TNF-α and IL-6 are sensitive markers of SLE disease activity. They may be useful independent markers for prediction of SLE disease activity and to differentiate normal subjects from those having SLE. Possible therapeutic implications in the treatment of SLE in the future deserve wide scale trials.

Future Directions
anti-TNFα treatment

An alternative way to directly target immune cells is to interfere with their messengers, the cytokines

Infliximab (Remicade®, Schering Plough, USA)

1-Six SLE patients with arthritis and/or nephritis were treated with four infusions of infliximab (300 mg each in combination with methotrexate or AZA).

Allpatients were refractory to standard therapy.

All patients completed the study at 52 weeks.

In all patients, significant improvement in clinical manifestations was observed including amelioration or proteinuria.

However, simultaneously a slight rise in anti-DNA and IgM cardiolipin antibody level was seen in four patients.

Toxicity was restricted to infections, mainly of the urinary tract.

None of the patients had an infusion reaction or an increase in SLE activity while receiving infliximab and or during the follow-up.

All the patients with arthritis presented a significant but transient improvement with relapses at 8-11 weeks after the infusion.

Moreover, in all patients with nephritis, proteinuria decreased and remained at a low level for at least 6 months after the last infusion of mAb.

Aringer M, *Arthritis Rheum 2004; 50: 3161-9*

2-A total of 13 lupus nephritis patients showed that short-term induction therapy at a dose of 5 mg/kg of infliximab was effective for years without flare up in lupus nephritis.

However, long-term infusion was associated with severe adverse events, for example central nervous system (CNS) lymphoma and Legionella pneumonia in two three SLE patients

Aringer et al. (2007) *Arthritis Rheum., 56(1), 274-9.*

.

Future Directions

Agents directed against tumor- necrosis factor alpha (TNFα)

3-Recently, reported on the safety and efficacy of infliximab given to a patient with active lupus with diffuse proliferative nephritis (WHO Class IV).

The patient failed to remit with a combination of full-dose steroids, mycophenolate mofetil and cyclosporine. However, she went to sustained remission with the addition of infliximab infusions

Hayat *et al*. *Clin. Rheumatol* 2007., *26(6), 973-975.*

4-Nine SLE patients treated with infliximab at 3 mg/kg of body weight :

four dropped out due to infliximab infusion reactions;

Five patients showed improvement in disease activity (SLEDAI) compared with 18 patients who received standard care .

No safety issues were reported except for infusion reactions in four patients.

Uppal SS. *Lupus 2009; 18: 690-7*

6-Nine Japanese patients

Refractory lupus nephritis

200mg of infliximab on three occasions.

One subject dropped out of the study because of pyelonephritis after the first infusion.

Proteinuria and disease activity of SLE improved significantly in six out of eight subjects

Matsumura et al. 2009

5-Currently, a trial of infliximab in lupus membranous nephritis is in progress (http://www.clinicaltrials.gov).

Anyone **WHO ISN**'t confused really doesn't understand the situation.

Edward R. Murrow

The Road Map

Histopathology of Lupus Nephritis

Conventional Therapies

Future Therapy

Conclusion

Conclusions and Future Perspectives

- **Intensive research in recent years has increased our understanding of the pathogenesis of SLE. As a consequence, new therapeutic approaches and possibilities are being explored to find better treatment possibilities which will be more effective, more specific and less toxic.**

- **The treatment of lupus nephritis today is markedly different, and objectively more effective, than it was 10 years ago.**

- **The hope and expectation is that a similar claim will be made 10 years .**

Conclusions and Future Perspectives

- **Biologics specifically targeting the pathways involved in this pathophysiological condition are continuously becoming developed.**
- **Experts see great promise in Bcell-targeted therapy, especially belimumab.**
- **In addition, anticytokine therapies against IL-6,INF-a, have offered possibilities for the future using new pathways for the treatment of lupus.**

Thank You

Alaa